JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Coexistent Multiple Myeloma or Increased Bone Marrow Plasma Cells Define Equally High-Risk Populations in Patients With Immunoglobulin Light Chain Amyloidosis

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ABSTRACT

Purpose
There is consensus that patients with light chain (AL) amyloidosis with hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria) also have multiple myeloma (MM). The aim of this study was to examine the spectrum of immunoglobulin AL amyloidosis with and without MM, with a goal of defining the optimal bone marrow plasma cell (BMPC) number to qualify as AL amyloidosis with MM.

Patients and Methods
We identified 1,255 patients with AL amyloidosis seen within 90 days of diagnosis between January 1, 2000, and December 31, 2010. We defined a population of patients with coexisting MM on the basis of the existence of CRAB criteria (AL-CRAB). Receiver operating characteristic analysis determined the optimal BMPC cut point to predict for 1-year mortality in patients with AL amyloidosis without CRAB to produce two additional groups: AL only ($\leq$ 10% BMPCs) and AL plasma cell MM (AL-PCMM; > 10% BMPCs).

Results
Among the 1,255 patients, 100 (8%) had AL-CRAB, 476 (38%) had AL-PCMM, and 679 (54%) had AL only. Their respective median overall survival rates were 10.6, 16.2, and 46 months ($P < .001$). Because the outcomes of AL-CRAB and AL-PCMM were similar, they were pooled for univariate and multivariate analyses. On multivariate analysis, pooled AL-CRAB and AL-PCMM retained negative prognostic value independent of age, Mayo Clinic AL amyloidosis stage, prior autologous stem-cell transplantation, and difference between the involved and uninvolved free light chain.

Conclusion
Patients with AL amyloidosis who have more than 10% BMPCs have a poor prognosis, similar to that of patients with AL-CRAB, and should therefore be considered together as AL amyloidosis with MM.

J Clin Oncol 31:4319-4324. © 2013 by American Society of Clinical Oncology

INTRODUCTION

There is consensus that patients with immunoglobulin light chain (AL) amyloidosis and hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria) also have multiple myeloma (MM). AL amyloidosis can coexist in patients with newly diagnosed MM[1,2] and is included in the definition of symptomatic MM of the International Myeloma Working Group (IMWG) as one of the criteria for organ/tissue impairment.[3,4] Although the median percentage of bone marrow plasma cells (BMPCs) among patients with AL amyloidosis is 7% to 10%,[5,6] the range is large. Different authors have used various cut points as thresholds to assign the moniker AL amyloidosis with associated MM, but in routine practice and clinical trials, the BMPCs have largely been ignored as a prognostic factor or as a parameter that might direct therapy. Emerging data on the prognostic value of higher levels of serum immunoglobulin free light chains (FLCs) are reminders of the potential influence of tumor burden on outcome.[6-8] We therefore designed a study to evaluate the spectrum of AL amyloidosis with and without MM.

PATIENTS AND METHODS

Between January 2000 and December 2010, 1,255 patients with systemic AL amyloidosis were evaluated at the Mayo Clinic (Rochester, MN) within 90 days of diagnosis. Patients whose exact date of diagnosis was not known were

Table 1. Demographics and Clinical Characteristics of Patients							
	AL Only (n = 679)		AL-PCMM (n = 476)		AL-CRAB (n = 100)		
Characteristic	No.	%	No.	%	No.	%	P
Characteristic							
Male	417	61	295	62	58	58	< .001
Age, years							.18
Median	62		63		65		
Range	25-92		30-89		34-90		
Diagnosed after 2005	425	63	272	57	50	50	< .001
Serum hemoglobin, mg/dL							< .001
Median	13.2		13		11.4		
Range	5.6-18.7		8.3-17.7		7.7-15.6		
Hemoglobin < 10 mg/dL (or < 2 mg/dL below normal)	80	12	54	12	38	38	< .001
Calcium > 11 mg/dL	6	0.9	1	0.2	11	11	< .001
Serum alkaline phosphatase, U/L							.08
Median	112		121		115		
Range	24-3,467		38-3,963		44-1,308		
Serum creatinine, mg/dL							.06
Median	1.2		1.1		1.2		
Range	0.6-10.3		0.4-7.6		0.4-7.1		
Creatinine > 1.3 mg/dL	101	15	52	11	20	20	.03
Serum albumin, g/dL							< .001
Median	2.8		2.9		3.1		
Range	0.7-4.9		0.6-4.5		1.3-4.5		
Lambda restricted	528	78	353	74	58	58	< .001
dFLC, mg/dL							< .001
Median	13.98		33.4		76.5		
Range	0.03-1,529		0.18-2,077		1.62-2,330		
β_2-microglobulin, μg/mL							< .001
Median	3.1		3.1		5.5		
Range	1-48.7		1.1-35.5		1.5-71		
NT-proBNP, pg/mL							.002
Median	1,838		3,290		3,964		
Range	7-70,000		35-70,000		27-39,860		
cTnT, ng/mL							< .001
Median	0.02		0.03		0.05		
Range	0.001-1.3		0.001-2.1		0.01-0.9		
2004 Mayo AL amyloidosis stage*							.01
Median	2		2		3		
Range	1-3		1-3		1-3		
I	90	22	34	14	3	8	
II	141	35	107	42	13	34	
III	172	43	111	44	22	58	
2012 Mayo AL amyloidosis stage†							< .001
Median	1		2		2		
Range	0-3		0-3		0-3		
I	114	29	42	17.5	3	8	
II	86	22	54	22.5	7	20	
III	95	25	61	25	8	22	
IV	94	24	83	25	18	50	
Bone lesions	51	8	30	7	69	69	< .001
BMPCs							< .001
Median	6		18		40		
Range	0-10		10.2-80		2-100		

NOTE. AL only: immunoglobulin light chain (AL) amyloidosis with ≤ 10% bone marrow plasma cells (BMPCs); AL-PCMM, AL amyloidosis with > 10% BMPCs; AL-CRAB, AL amyloidosis with hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria).

Abbreviations: cTnT, cardiac troponin T; dFLC, difference between involved and uninvolved free light chains; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

*2004 Mayo AL amyloidosis stage defined by cTnT and NT-proBNP threshold (0.035 ng/mL and 332 pg/mL, respectively). Stage I, both below threshold; stage II, either above threshold; stage III, both above threshold.

†2012 Mayo AL amyloidosis stage defined by cTnT, NT-proBNP, and dFLC threshold (0.05 ng/mL, 1,800 pg/mL, and 18 mg/dL, respectively). Stage I, all below threshold; stage II, three below threshold; stage III, two below threshold; stage IV, none below threshold.

excluded. Clinical laboratory and treatment data were extracted from a prospectively maintained database. The Mayo Foundation institutional review board approved the study, and all patients consented to have their medical records reviewed according to institutional review board practices. Patients with pretreated AL amyloidosis or MM and patients with AL amyloidosis due to a lymphoproliferative disorder were excluded from the analysis as were patients with MM with incidental positive bone marrow or fat but with no amyloid-specific syndrome.[2] The diagnosis of AL amyloidosis was predicated on the presence of organ involvement as previously defined[9] in addition to a tissue biopsy specimen that stained positive with Congo red and exhibited green birefringence under polarized light and was documented to be AL amyloid by typing with immunohistochemistry, immunofluorescence, or mass spectrometry. Follow-up data were available on all patients. The level of BMPCs was the highest estimate of plasma cells from the aspirate, the biopsy, or a slide-based plasma cell labeling index.[10] First-line treatment data were available for 1,005 patients: 502 (50%) received melphalan, 77 (8%) immunomodulatory drugs, 34 (3%) proteasome inhibitors, and 64 (6%) steroids only; 37 patients (3%) received other forms of chemotherapeutic agents including investigational drugs, seven patients (0.7%) received no treatment, and the remaining 284 patients (28%) received combination regimens.

The patients were classified as AL-CRAB if they had hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria), as previously defined,[3] attributable to plasma cell disorder. The individual patients' records were reviewed to assign attribution. Alternate causes of CRAB positivity that could not be attributed to clonal plasma cell expansion included but were not limited to anemia of chronic disease, blood loss, presumed amyloid nephropathy, as previously defined,[9,11] chronic kidney disease, hyperparathyroidism, osteoporosis, or isolated bone abnormalities not typical for MM. Patients were further stratified according to two previously reported amyloid staging systems: the 2004 Mayo AL amyloidosis staging system stratifies patients by cardiac troponin T and N-terminal pro–B-type natriuretic peptide thresholds (0.035 ng/mL and 332 pg/mL, respectively) as follows: stage I, both below threshold; stage II, either above threshold; and stage III, both above threshold.[7] The 2012 Mayo AL amyloidosis staging system stratifies patients by cardiac troponin T, N-terminal pro–B-type natriuretic peptide, and the difference between the involved and uninvolved free light chain (dFLC) thresholds (0.05 ng/mL, 1,800 pg/mL, and 18 mg/dL, respectively): stage I, all below threshold; stage II, two below threshold; stage III, one below threshold; and stage IV, none below threshold.[6]

Among patients without AL-CRAB, receiver operating characteristic (ROC) analysis was performed to determine the optimal BMPC cut point to predict for 1-year mortality in patients with AL amyloidosis without CRAB.

Thus, two additional groups were generated: AL only (BMPCs below or equal to the ROC-defined threshold) and AL plasma cell MM (AL-PCMM; BMPCs greater than the defined threshold). Survival was estimated by the method of Kaplan-Meier. The Pearson χ^2 test and the Kruskal-Wallis test were used to ascertain differences between nominal and continuous variables, respectively. A Cox proportional hazards regression model was used for multivariable analysis. P values less than .05 were considered significant. All statistical analyses were performed by using JMP software (SAS, Cary, NC).

RESULTS

There were 100 patients with AL-CRAB; for the remaining 1,155 patients, the ROC breakpoint of BMPCs for death at 1 year was 10.2%, and for death at 5 years, it was 12.5%. For the purposes of this study, the 10% cut point was chosen, leaving 476 (38%) with AL-PCMM (> 10% BMPCs), and 679 (54%) with AL only (≤ 10% BMPCs). The patients' clinical and laboratory features are listed in Table 1. Of the 1,155 patients without CRAB, 306 (27%) had at least one CRAB feature that was associated with causes other than MM. Patients with AL-CRAB were less likely to be lambda restricted. Cardiac biomarkers and 2012 Mayo AL amyloidosis stage were significantly worse in the AL-CRAB and AL-PCMM groups.

Patients with AL-CRAB had inferior median overall survival (OS) when compared with the rest of patients with AL amyloidosis (10.6 v 29 months; $P <$ .001; Fig 1A). As shown in Figure 1B, the OS for AL-PCMM was also only 16 months, which was comparable to that of the AL-CRAB group and markedly different from the 46 months of the AL-only group ($P <$ .001). Because outcomes often appear to be superior with autologous stem-cell transplantation (ASCT),[12] we next considered whether patients received ASCT as part of their treatment. Twenty-two patients (22%) with AL-CRAB, 138 (29%) with AL-PCMM, and 203 (30%) with AL only ($P =$ .79) had ASCT. For those patients who never received ASCT (Fig 2A), the 5-year OS rates were 11% (AL-CRAB), 19% (AL-PCMM), and 31% (AL only; $P <$ .001). In contrast, for those patients who received ASCT (Fig 2B), the respective 5-year OS rates were 54%, 46%, and 73% ($P <$ .001).
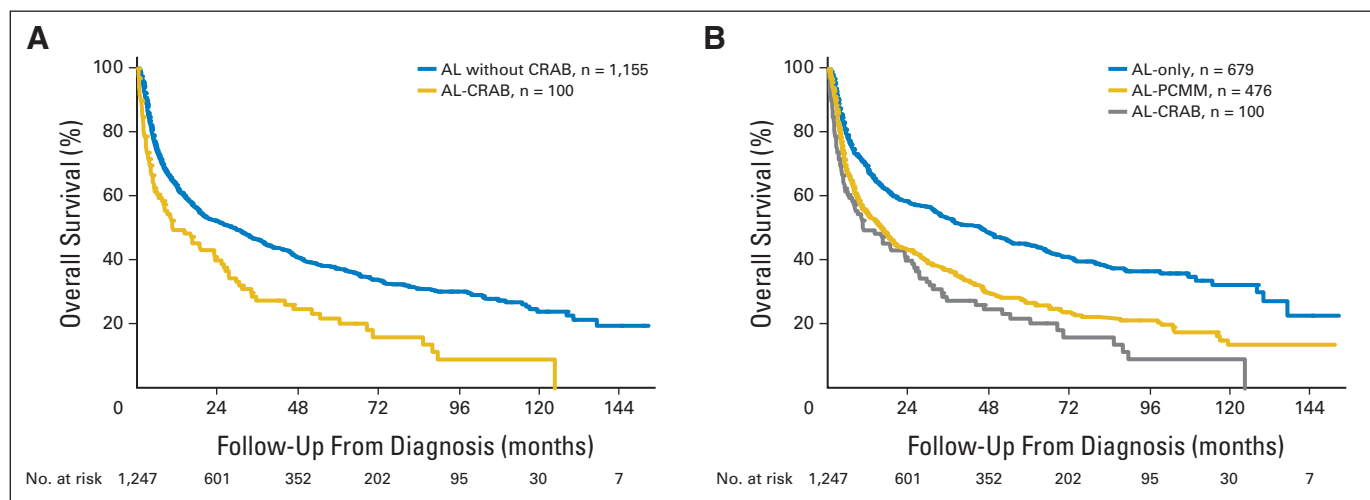

Fig 1. Kaplan-Meier curves for overall survival of patients with immunoglobulin light chain (AL) amyloidosis (A) with and without hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria) and (B) according to percentage of bone marrow plasma cells (BMPCs). AL-CRAB, AL amyloidosis with CRAB; AL-only, AL amyloidosis with ≤ 10% BMPCs; AL-PCMM, AL amyloidosis with > 10% BMPCs.
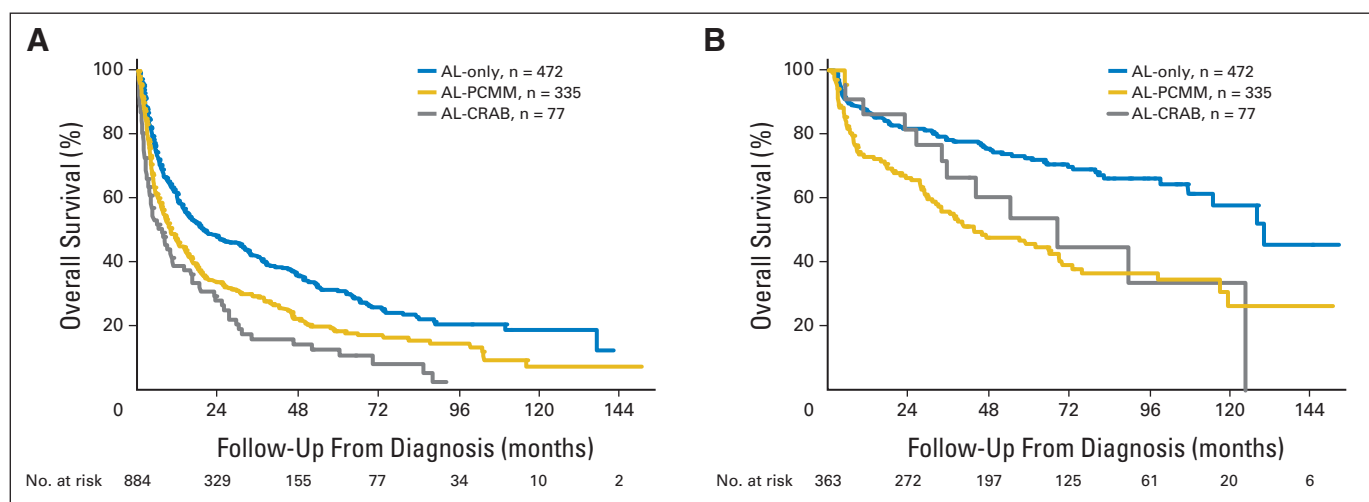
Fig 2. Kaplan-Meier curves for overall survival of patients with immunoglobulin light chain (AL) amyloidosis who (A) did not have autologous stem-cell transplantation and (B) did have autologous stem-cell transplantation. AL-CRAB, AL amyloidosis with hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria); AL-only, AL amyloidosis with ≤ 10% bone marrow plasma cells; AL-PCMM, AL with > 10% bone marrow plasma cells.

Univariate and multivariate analyses were performed to elucidate interactions between BMPCs and other variables. On univariate analysis, OS was predicted by age ($P < .001$), dFLC more than 18 mg/dL (as used in the 2012 Mayo AL amyloidosis staging system; $P < .001$), 2004 Mayo AL amyloidosis stage ($P < .001$), 2012 Mayo AL amyloidosis stage ($P < .001$), history of ASCT ($P < .001$), AL-CRAB versus AL only ($P < .001$), and AL-PCMM versus AL only ($P < .001$), but not AL-CRAB versus AL-PCMM ($P = .08$). Because outcomes were similar for AL-PCMM and AL-CRAB, they were pooled for the multivariate analyses. Two multivariate models were built, one with the 2012 Mayo AL amyloidosis staging system and another with the 2004 Mayo AL amyloidosis staging system. On multivariate analysis, pooled AL-CRAB and AL-PCMM retained negative prognostic value as did age, Mayo AL amyloidosis stage, dFLC, and history of ASCT (Table 2).

DISCUSSION

In this study, we described the spectrum of AL amyloidosis and showed that those patients with AL amyloidosis who have more than 10% BMPCs have a prognosis similar to that of patients with AL amyloidosis with CRAB. This finding would suggest that these two entities be considered together as AL amyloidosis with MM in both observational reports and, more importantly, in prospective therapeutic trials. The notion that AL amyloidosis with MM has a worse prognosis is not a new concept,[13-15] but this point has seemingly been lost. In prospective therapeutic clinical trials, only the AL-CRAB group has been considered as having MM. This small group (8% of the current data set) is excluded from most prospective therapeutic trials,

Table 2. Results of Univariate and Multivariate Analyses of Various Prognostic Factors

Prognostic Factor	Univariate			Multivariate 1*			Multivariate 2†		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Age	1.03	1.02 to 1.04	< .001	1.02	1.01 to 1.03	.001	1.02	1.01 to 1.03	.001
2004 Mayo AL amyloidosis stage‡	2.6	2.2 to 3.1	< .001	2.25	1.9 to 2.7	< .001	Not included		
2012 Mayo AL amyloidosis stage§	1.9	1.7 to 2.1	< .001	Not included		< .001	1.7	1.5 to 1.9	< .001
Prior ASCT	0.35	0.29 to 0.42	< .001	0.53	0.39 to 0.7	< .001	0.6	0.4 to 0.73	< .001
dFLC > 18 mg/dL	2.3	1.9 to 2.7	< .001	1.4	1.1 to 1.8	< .001	Not included		
AL-PCMM v AL only	1.6	1.38 to 1.85	< .001	Not included			Not included		
AL-CRAB v AL only	2.0	1.57 to 2.54	< .001	Not included			Not included		
AL-CRAB v AL-PCMM	1.25	0.97 to 1.6	.08	Not included			Not included		
Pooled AL-CRAB and AL-PCMM v AL only	1.7	1.44 to 1.9	< .001	1.37	1.1 to 1.68	.004	1.28	1.04 to 1.57	.02

NOTE. AL only: immunoglobulin light chain (AL) amyloidosis with ≤ 10% bone marrow plasma cells; AL-PCMM, AL amyloidosis with > 10% bone marrow plasma cells; AL-CRAB, AL amyloidosis with hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria).
Abbreviations: ASCT, autologous stem-cell transplantation; dFLC, difference between involved and uninvolved free light chains; RR, risk ratio.
*Multivariate 1 includes 2004 Mayo AL amyloidosis stage but excludes Mayo 2012 stage because of redundancy of variables.
†Multivariate 2 includes 2012 Mayo AL amyloidosis stage but excludes 2004 Mayo AL amyloidosis stage and dFLC because of redundancy of variables.
‡2004 Mayo AL amyloidosis stage defined by cardiac troponin T and N-terminal pro–B-type natriuretic peptide threshold (0.035 ng/mL and 332 pg/mL, respectively). Stage I, both below threshold; stage II, either above threshold; stage III, both above threshold.
§2012 Mayo AL amyloidosis stage defined by cardiac troponin T, N-terminal pro–B-type natriuretic peptide, and dFLC threshold (0.05 ng/mL, 1,800 pg/mL, and 18 mg/dL, respectively). Stage I, all below threshold; stage II, three below threshold; stage III two below threshold; stage IV, none below threshold.

but the 38% of patients with AL-PCMM are routinely pooled into small phase II trials and larger phase III trials with no consideration of BMPC involvement. The 2012 Mayo AL amyloidosis staging system[6] incorporates serum dFLC, which alludes to BMPC burden but does not capture the entire risk of tumor biology, as is evidenced by the following three observations: (1) 42% of patients with AL only have a dFLC of more than 18 mg/dL; (2) 33% of patients with AL-PCMM have a dFLC of less than 18 mg/dL; and (3) on multivariate analysis, AL-PCMM was an independent prognostic factor, even when the 2012 Mayo AL amyloidosis staging system was included.

It is intriguing that 10% to 12% BMPCs was the statistically derived threshold for risk of death among patients with AL amyloidosis, since 10% BMPCs is the same percentage that is used to distinguish smoldering MM from monoclonal gammopathy of undetermined significance (MGUS). Our definition varies slightly since we included the 115 patients without CRAB but with 10% BMPCs in the AL-only group, whereas when assigning MGUS versus MM outside the context of AL amyloidosis, these patients would have been considered as having MM. The threshold effect of 10% BMPCs would suggest that once BMPCs find the means by which they can expand their niche beyond 10%, they have a different biology and relationship with the bone marrow microenvironment. The relationship between MM and AL amyloidosis is complex. AL amyloidosis can be found in newly diagnosed[2] patients with MM or can develop later in their disease course,[16] which bodes poorly for these patients.[17] Historically, the converse—that is, patients with AL amyloidosis developing CRAB-positive MM years after their AL amyloidosis diagnosis—is rare, presumably because patients' life spans were too short to allow for clonal evolution.[18]

The significance of increased BMPCs in AL amyloidosis biology is not clear. Plasma cells in AL amyloidosis usually have a low proliferative index,[19] and the clinical picture is dominated by organ dysfunction resulting from amyloid deposition rather than from clonal progression.[20] The fact that those patients with the highest BMPCs were also some of the same patients who had the most advanced cardiac disease makes one wonder whether these were the patients who for years had unrecognized MGUS-level BMPCs with an "unlucky protein"[2] that was insidiously forming AL fibrils, but who then experienced a transformational event to their BMPCs—perhaps the exact repertoire of transformational events that patients progression from standard MGUS to smoldering MM to MM experience. These transformed BMPCs, now capable of expanding their numbers within the bone marrow space, not only increased the production of AL precursor protein thus fueling the forward reaction of amyloid formation and organ dysfunction, but are also less well suited to being eradicated long-term by current chemotherapies, including ASCT.

Although previous authors have suggested that increased BMPCs in AL amyloidosis have prognostic value and are associated with more amyloidogenic FLCs and organ involvement,[6-8] the relative significance of coexistent MM was not addressed. Herein, we demonstrate that the extent of BMPCs is of paramount importance in predicting outcome in patients with newly diagnosed AL amyloidosis. These findings should affect future clinical trial design, potentially allowing patients with AL-CRAB to enroll onto AL amyloidosis trials along with patients who have AL-PCMM, but including the presence of coexisting MM as either a stratification factor or, at a minimum, as a descriptive factor. This adjustment, however, should not extend to those patients with MM who do not have clinical organ involvement by amyloid but who do have an incidentally found positive Congo red staining of the bone marrow or fat. We found 16 of these patients during data abstraction who had a median survival of 57 months.

Limitations of our study include its retrospective nature and potentially the way AL-CRAB was defined, since the adjudication of CRAB features to MM is a clinical decision. Particular attention was paid to CRAB adjudication as the medical records were abstracted. When calculating BMPCs, we used the highest estimate of plasma cells from the aspirate, the biopsy, or slide-based plasma cell labeling index. In patients with MM, the highest estimate of BMPCs is the best predictor of complete remission, progression-free survival, and OS following ASCT.[9] Although it is not known whether this is also true for AL amyloidosis, comparing bone marrow aspirates can be challenging because of dilution with peripheral blood. Using the highest estimate helped overcome this confounding factor so that the definition of BMPC percentage is consistent in all marrow examinations. Another potential limitation was the choice of the 1-year mark for our ROC analysis, since short-term survival might not predict well for long-term outcomes; however, long-term survival is dramatically affected by what happens in year 1 since 40% to 50% of newly diagnosed patients die within the first year.[21] Moreover, 12.5% BMPCs predicted for 5-year OS on ROC analysis.

In conclusion, we provide evidence that patients with AL amyloidosis with MM defined either by CRAB or by more than 10% BMPCs have a similarly poor prognosis and, as a practical matter, could be considered as one group. In aggregate, this study illustrates the complex interactions among plasma cell biology/burden, extent of cardiac insult, and therapy. We do not propose that patients with AL-PCMM and those with AL-CRAB be treated exactly like patients with MM, since we know that the presence of AL organ involvement increases these patients' risk for drug toxicity and treatment-related mortality. Rather, we hope that patients with AL-CRAB will be considered for clinical trials in general, and that they, along with the patients with AL-PCMM, may be the focus of specific trials that address whether the benefit of more myeloma-like therapy outweighs the risks.

AUTHOR CONTRIBUTIONS

Collection and assembly of data: Taxiarchis V. Kourelis, Shaji K. Kumar, Martha Q. Lacy, Francis K. Buadi, Suzanne R. Hayman, Steven Zeldenrust, Nelson Leung, Robert A. Kyle, Stephen Russell, David Dingli, John A. Lust, Yi Lin, Prashant Kapoor, S. Vincent Rajkumar, Arleigh McCurdy

Data analysis and interpretation: Taxiarchis V. Kourelis, Shaji K. Kumar, Morie A. Gertz, Angela Dispenzieri

Manuscript writing: All authors
Final approval of manuscript: All authors

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